EMERGING AND RE-EMERGING INFECTIOUS DISEASES

Despite remarkable advances in medical research and treatments during the 20th century, infectious diseases remain among the leading causes of death worldwide for three reasons: (1) emergence of new infectious diseases, (2) re-emergence of old infectious diseases, and (3) persistence of intractable infectious diseases. Emerging diseases include outbreaks of previously unknown diseases or known diseases whose incidence in humans has significantly increased in the past two decades. Re-emerging diseases are known diseases that have reappeared after a significant decline in incidence. Within the past two decades, innovative research and improved diagnostic and detection methods have revealed a number of previously unknown human pathogens. (For a list of emerging and re-emerging infectious diseases and pathogens, see the table below or *www.niaid.nih.gov/dmid/eid.)* Largely as a result of better detection methods, evidence also is accumulating that infective agents play a role in diseases previously thought to be chronic and noncommunicable. For example, during the past decade, chronic gastric ulcers, which formerly were thought to be caused by stress or diet, were found to be the result of infection by the bacterium *Helicobacter pylori.*

New infectious diseases continue to evolve and "emerge." Changes in human demographics, behavior, land use, and other factors are contributing to new disease emergence by changing transmission dynamics to bring people into closer and more frequent contact with pathogens. This situation may involve exposure to animal or arthropod carriers of disease. Increasing trade in exotic animals for pets and as food sources has increased opportunities for pathogens to jump from animal reservoirs to humans. For example, close contact with exotic rodents imported to the United States as pets led to the recent outbreak of monkeypox in this country, and use of exotic civet cats for meat in China was found to be the route by which the severe acute respiratory syndrome (SARS) coronavirus made the transition from animal to human hosts.

In addition to the continual discovery of new human pathogens, old infectious disease enemies are "re-emerging." Natural genetic variations, recombinations, and adaptations allow new strains of known pathogens to appear. The immune system has not been previously exposed to these new strains and therefore is not primed to recognize them (e.g., influenza). Furthermore, human behavior plays an important role in disease re-emergence. Increased and sometimes imprudent use of antimicrobial drugs and pesticides has led to the development of resistant pathogens, allowing many diseases that were formerly treatable with drugs to make a comeback (e.g., tuberculosis, malaria, hospital-acquired and food-borne infections). Recently, decreased compliance with vaccination policy also has led to re-emergence of diseases such as measles and pertussis, which were previously under control. The use of deadly pathogens such as smallpox or anthrax as agents of bioterrorism is an increasingly acknowledged threat to the civilian population. Moreover, many important infectious diseases have never been adequately controlled, on either the national or international level. Infectious diseases that have posed ongoing health problems in developing countries such as food- and water-borne infections, dengue, and West Nile virus, are re-emerging in the United States.

NIAID has developed a strategy to address the threat of emerging and re-emerging infectious diseases through targeted research and training. That strategy, which was initially outlined in the Institute's 1996 document, *The NIAID Research Agenda for Emerging Infectious Diseases (www.niaid.nih.gov/publications/execsum/bookcover.htm)*, was updated in the 2000 NIAID strategic plan, *NIAID: Planning for the 21st Century (www.niaid.nih.gov/strategicplan/pdf/splan.pdf)*. In May 2001, NIAID released *NIAID Global Health Research Plan for HIV/AIDS, Malaria, and Tuberculosis (www.niaid.nih.gov/publications/globalhealth/global.pdf)*. This document outlines the Institute's plans for the next decade for diagnosing, treating, and preventing these three infections and also lays out a plan for enhancing in-country research capacity.

Focus on

List of NIAID Emerging and Re-emerging Diseases 2003

Group I—Pathogens Newly Recognized in the Past Two Decades

Acanthamebiasis
Australian bat *Lyssavirus*
Babesia, atypical
Bartonella henselae
Cyclospora cayetanensis
Ehrlichiosis
Encephalitozoon cuniculi
Encephalitozoon hellem
Enterocytozoon bieneusi
Helicobacter pylori
Hendra or equine morbilli virus
Hepatitis C
Hepatitis E
Human herpesvirus 8
Human herpesvirus 6
Lyme borreliosis
Microsporidia
Parvovirus B19

Group II—Re-emerging Pathogens

Coccidioides immitis
Enterovirus 71
Prion diseases
SARS coronavirus
Streptococcus, group A
Staphylococcus aureus

Group III—Agents With Bioterrorism Potential

CDC—Category A

Bacillus anthracis (anthrax)
Clostridium botulinum
Francisella tularensis (tularemia)
Variola major (smallpox) and other pox viruses
Viral hemorrhagic fevers
- Arenaviruses
- Dengue
- Ebola
- Hantaviruses causing hantavirus pulmonary syndrome
- Lassa fever
- LCM, Junin virus, Machupo virus, Guanarito virus
- Marburg virus
- Rift Valley fever

Yersinia pestis

CDC—Category B

Brucella species (brucellosis)
Burkholderia mallei (glanders)
Coxiella burnetii (Q fever)
Epsilon toxin of *Clostridium perfringens*
Food-borne and Water-borne Pathogens
- Bacteria
  - *Campylobacter jejuni*
  - Diarrheagenic *E. coli*

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List of NIAID Emerging and Re-emerging Diseases 2003, *Continued*

Bacteria, *Continued*
- *Listeria monocytogenes*
- Pathogenic vibrios
- *Salmonella*
- *Shigella species*
- *Yersinia enterocolitica*

Protozoa
- *Cryptosporidium parvum*
- *Cyclospora cayatanensis*
- *Entamoeba histolytica*
- *Giardia lamblia*
- Microsporidia
- Toxoplasma

Viruses (calciviruses, hepatitis A)

Additional viral encephalitides
- California encephalitis
- Eastern equine encephalitis
- Japanese encephalitis virus
- Kyasanur Forest virus
- LaCrosse virus
- Venezuelan equine encephalitis
- Western equine encephalitis
- West Nile virus

CDC—Category B, *Continued*

Ricin toxin (from *Ricinus communis*)

Staphylococcal enterotoxin B

Typhus fever (*Rickettsia prowazekii*)

CDC—Category C

Emerging infectious disease threats such as Nipah virus, additional hantaviruses, and the following pathogens:
- Influenza
- Other rickettsias
- Multidrug-resistant tuberculosis (MDR-TB)
- Rabies
- Tick-borne encephalitis viruses
- Tick-borne hemorrhagic fever viruses
- Crimean-Congo hemorrhagic fever virus
- Yellow fever

Pathogens that naturally emerge with, or are engineered for, increased virulence, increased transmission, and/or the ability to evade the immune response. ❖

To an unprecedented extent, issues related to global health and infectious diseases are on the agendas of world leaders, health policymakers, and philanthropies. This attention has been focused both on scientific challenges such as vaccine development, and on the deleterious effects of infectious diseases on economic development and political stability.

To enhance the capacity to deal with the challenges posed by emerging diseases, NIAID opened a new biosafety level 3 (BSL-3) laboratory in Hamilton, Montana, in April 2002 and anticipates completion of a new BSL-3 laboratory in Rockville, Maryland, in early 2004. NIAID also is developing plans for a BSL-3 laboratory in the Bethesda, Maryland, area. These laboratories will enable the Institute to conduct BSL-3 animal studies and laboratory research on infectious agents such as drug-resistant *Mycobacterium tuberculosis (M.tb).* Research programs on pathogenic microorganisms, including *Borrelia, Yersinia,* the influenza virus, West Nile virus, and dengue virus, will be continued and expanded.

Likewise, in fiscal year (FY) 2003 NIAID established several new extramural programs

that will address needs for biodefense and emerging infectious disease research:

- National Biocontainment Laboratories (NBLs) and Regional Biocontainment Laboratories (RBLs). The construction of two NBLs that will provide BSL-4 facilities for researchers was funded in September 2003. The construction is expected to take up to 5 years. The construction of nine RBLs, which will provide BSL-3 facilities for regions throughout the country, was funded and is expected to take from 2 to 3 years.

- Eight Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases Research (RCE) grants were funded in September 2003. These RCEs, which will be located throughout the country, are consortia of institutions, usually within a single region. They are funded to develop and maintain strong infrastructure and to carry out multifaceted research and development activities that will provide the scientific information and translational research capacity to make the next generation of therapeutics, vaccines, and diagnostics against the NIAID Category A, B, and C agents. Two planning grants for RCEs were funded to enable institutions to develop consortia for the study of these pathogens and to support research program initiation and resource acquisition.

- NIAID's Biodefense and Emerging Infections Research Resources Program will support the acquisition, authentication, storage, and distribution to the scientific community of state-of-the-art research and reference reagents related to biodefense and emerging infectious diseases, starting in late FY 2003. Included will be the capability to validate, expand, and produce biological agents, including cell lines, clones, proteins, monoclonal and polyclonal antibodies, and diagnostic tools.

- *In Vitro* and Animal Models for Emerging Infectious Diseases and Biodefense will provide a range of resources for preclinical testing of new therapies and vaccines, including nonhuman primate models. Under these new contracts, task orders for small animal and nonhuman primate models for anthrax will be developed and validated for Food and Drug Administration (FDA) licensure of vaccines and therapeutics against inhalational anthrax. This activity will entail safety, toxicology, and pharmaceutical testing in small and large animals, including the capability for conducting challenge studies. Future task order awards will develop, validate, and use models for other Category A, B, and C pathogens.

- The Food and Waterborne Diseases Integrated Research Network expands the Institute's capacity to conduct clinical research studies of food- and water-borne enteric pathogens. Through one of the Microbiology Research Units (MRU) with a botulism research center, NIAID is determining the pharmacokinetics of botulinum toxins and antitoxins in several animal models. These data will be helpful for the development, formulation, and use of equine-based antitoxins and will serve as a basis for next-generation antitoxins.

Basic and clinical research is critical to the development of a national strategy to confront these microbial challenges. Such research increases our collective understanding of ever-changing microbial populations and permits this new knowledge to be transformed into better diagnostics, vaccines, and therapies.

Basic research and research training also are the foundation for surveillance and response activities.

During 2003, NIAID supported research initiatives on biodefense as well as on emerging and re-emerging infectious diseases in multiple areas, including TB, Lyme disease, influenza, prion diseases, and other infectious diseases and deadly pathogens.

Emerging and Re-emerging Infectious Diseases

Severe Acute Respiratory Syndrome—SARS

In spring 2003, the world became aware of an outbreak of a newly recognized pneumonia that was named "severe acute respiratory syndrome," or SARS. The outbreak is thought to have begun in southeastern China's Guangdong province in November 2002, with subsequent spread to the special administrative region of Hong Kong by February 2003. Significant outbreaks also occurred in other Asian countries such as Vietnam and Singapore, and in Canada. Epidemiologic investigation showed that the disease disproportionately affected healthcare workers and other close contacts of patients such as family members. Through an NIAID-supported contract with Dr. Robert Webster at St. Jude Children's Research Hospital in Memphis, researchers at Hong Kong University and their colleagues at four local hospitals were the first to report to the World Health Organization the isolation of a virus that was linked conclusively to SARS patients. Using a high-powered microscope, researchers examined a culture from a lung biopsy sample and found virus particles whose surface was studded with an array of proteins resembling a crown around the virus—a "coronavirus." The researchers then used antibody tests and other molecular tools to confirm that that this deadly coronavirus was present in at least 35 of the SARS patients they were studying.

Before the emergence of SARS, human coronaviruses were predominately associated with up to 30 percent of common colds. Coronaviruses are the largest single-stranded RNA viruses known and are divided into three serogroups. Recent data indicate that SARS is the prototype strain for a new fourth group of coronaviruses.

In response to the need for rapidly increased research on the SARS coronavirus, in FY 2003 NIAID awarded administrative supplements to grantees to expand activities on the basic biology and immunology of coronaviruses. NIAID also supported contracts to develop diagnostics, vaccines, and therapeutics for SARS. In addition, NIAID supports epidemiologic work on SARS and conducts SARS research within its intramural program. Highlights include the following:

- NIAID Division of Intramural Research (DIR) scientists have studied the replication of the SARS coronavirus in mice and nonhuman primates. They found that the virus replicates in the respiratory tracts of both these animal models to levels that will permit an evaluation of the efficacy of vaccines, immunotherapeutics, and antiviral drug treatment strategies. In the mouse model, primary infection provided protection from re-infection, and antibody alone protected against viral replication. These observations suggest that vaccines that induce neutralizing antibodies and strategies for immunoprophylaxis or immunotherapy are likely to be effective. Candidate vaccines and immunoprophylaxis strategies will be evaluated in mice and nonhuman primates;

animal models for the study of disease pathogenesis also will be pursued.

- NIAID, in collaboration with the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) and the Centers for Disease Control and Prevention (CDC), is supporting the *in vitro* screening of candidate drugs against the SARS coronavirus. Investigators have screened more than 1,400 compounds, including all FDA-approved antiviral drugs. Although several approved drugs have shown moderate activity against the virus, they do so only at concentrations that are toxic to humans. Classes of experimental compounds that have shown activity and will be studied further are cysteine proteinase inhibitors and interferons.

- NIAID awarded five contracts, grants, and supplements to companies and researchers towards development of vaccines for SARS, covering a variety of different vaccine approaches.

- NIAID-supported researchers at Hong Kong University have developed a polymerase chain reaction assay for detection of the SARS coronavirus. The test has been shown to detect the SARS virus in respiratory aspirates and fecal samples.

- NIAID is supporting the development of a diagnostic microarray that will be able to detect influenza, SARS, and other respiratory viruses.

- NIAID has expanded its Pandemic Preparedness in Asia contract with St. Jude Children's Research Hospital (Dr. Robert Webster, Principal Investigator) to do the following:

  - Expand efforts to identify the animal reservoirs for coronaviruses in Asia;

  - Establish cell-based laboratory assays to assess the immune response in infected patients; and

  - Conduct seroepidemiologic studies of family members and other close contacts of SARS patients to assess the rates of asymptomatic infections.

- NIAID is supporting the generation and distribution of a variety of SARS reagents for the research community, including the following:

  - **Overlapping peptides.** The NIH AIDS Research and Reference Reagent Program developed important tools for researchers to help understand the immune response to the SARS virus. One of these tools, a set of synthetic overlapping peptides covering the N, M, and S genes of the SARS virus, can be used to map the T cell responses in exposed and infected people. Use of these peptides will help to determine whether SARS patients with different disease outcomes have quantitatively different T cell responses to viral proteins.

  - **SARS microarrays.** NIAID's Pathogen Functional Genomics Resource Center has developed microarrays that contain genetic sequences of SARS coronavirus isolates from the United States, Canada, and Asia, which can be used to detect tiny genetic variations in the SARS viruses. With this information and information on the clinical outcomes of patients infected with SARS, scientists hope to determine which strains are most dangerous and to gain information on the development of antiviral drugs. (See "NIAID Offers 'SARS Chip' Free to Researchers" on page 93 for more information.)

- NIAID has issued a number of solicitations for grant and contract proposals that will further expand research on SARS and accelerate product development. These new programs will include development of diagnostics, vaccines, and therapeutics for SARS and will provide opportunities for partnerships between academia, Government, and the private sector.

For more information on SARS research updates and opportunities, please visit *www.niaid.nih.gov/dmid/sarsopps.htm* and *www.niaid.nih.gov/factsheets/sars.htm.*

West Nile Virus

NIAID supports a robust West Nile virus research portfolio. The following points summarize key research in several different areas:

- Basic research leads to a better understanding of the host, pathogen, and environmental factors that influence disease emergence. Basic research determines which flavivirus proteins contribute to the virus's ability to cause disease and examines how protective immune responses are elicited within the central nervous system during acute flavivirus encephalitis.
- A golden hamster model has been developed by NIAID-supported researchers and is used for screening drugs and for examining factors that contribute to immunity. This model has proven useful in evaluating strategies for preventing the complications associated with this emerging infectious disease.
- In 1999, NIAID funded a fast-track project to develop a candidate West Nile virus vaccine with Acambis, Inc. Since then, scientists have developed a prototype vaccine and conducted initial feasibility studies. The vaccine is a chimeric vaccine (West Nile virus protein on a yellow fever vaccine). The Acambis West Nile virus vaccine candidate has so far demonstrated good safety, efficacy, and protection against disease in animal models. Phase I clinical trials in humans were initiated in 2003 by Acambis.
- A DNA vaccine is being supported by NIAID.
- NIAID has funded investigators to establish a system to screen chemical compounds for possible antiviral activity against West Nile virus. Approximately 500 compounds have been screened, and several have moved forward to preclinical evaluation. NIAID also is supporting research on immunotherapeutics.
- NIAID supports the World Reference Center for Arboviruses, which has reference anti-West Nile sera and seed lots of various strains of West Nile virus. These reagents were provided when requested by investigators in the United States and Canada.
- At the end of FY 2002, the Division of Microbiology and Infectious Diseases (DMID) awarded two contracts to establish Emerging Viral Diseases Centers in response to a Request for Proposal titled "U.S. Based Collaboration in Emerging Viral and Prion Diseases." Each contract establishes broad-based, interactive, multidisciplinary research teams with the scientific expertise needed to study the emergence of a wide variety of zoonotic and arthropod-borne viral pathogens and other emerging viral threats. Both contracts also provide capacity to redirect funds and resources in the event of an urgent public health threat from either natural disease or bioterrorist release.

Under this provision, research on the newly discovered SARS coronavirus is being conducted at both sites. These contracts cover several important areas of research, including basic biology of the virus, West Nile virus ecology and pathogenic/epidemic potential, diagnosis, prevention, and therapy.

- NIAID supports research aimed at better understanding the vectors of transmission in affected areas. Such an understanding will allow improved monitoring and surveillance for the vectors and the viruses they transmit. NIAID also supports the development and preliminary testing of vector control strategies.

NIAID intramural scientists also have developed a West Nile virus vaccine candidate, which they have tested in monkeys with promising results. This vaccine candidate is a result of groundbreaking studies conducted more than a decade ago, in which NIAID scientists combined parts of different flaviviruses (a family of viruses that includes West Nile virus, dengue, Japanese encephalitis, and others) to make them weaker and thus more suitable for a live-virus vaccine. The West Nile virus vaccine uses part of the dengue virus as a backbone to which protective antibody-eliciting components of the West Nile virus are added. A supply of this vaccine suitable for human use has been prepared, and phase I human trials are planned for 2004. Development of other vaccine approaches, such as a full-length cDNA-derived West Nile virus vaccine, is under way.

For more information on West Nile virus and NIAID's research portfolio in this area, see *www.niaid.nih.gov/publications/wnile/default.htm* and *www.niaid.nih.gov/factsheets/westnile.htm.*

Tuberculosis

M.tb kills more people globally than any other single infectious agent. It is estimated that one-third of the world's population (1.86 billion people) are infected with *M.tb*, and 16.2 million people currently have tuberculosis (TB).[36,37] In 1999, an estimated 8.4 million persons developed TB, and 2 to 3 million patients died from this disease. Based on these statistics, TB kills more adults globally than any other single infectious agent.[38]

The majority of TB cases occur in developing nations. Although TB is essentially a treatable disease, lack of availability of drugs in many countries and poor adherence to treatment schedules due to side effects and the long duration of treatment (6 to 12 months) have resulted in the development of single drug-resistant and multidrug-resistant TB (MDR-TB) strains producing TB that is much more difficult to cure. Furthermore, the link between HIV and TB is believed to be a major factor in the spread of TB. In 1997, of the 1.86 billion individuals worldwide who were infected with *M.tb*, approximately 10.7 million also were infected with HIV. In Africa, TB cases are increasing by 10 percent each year because of HIV. These factors, combined with a suboptimal public health infrastructure in many countries, contribute to the ongoing spread and re-emergence of TB worldwide. (For additional information on NIAID TB research, see page 133.)

Lyme Disease

Lyme disease (borreliosis) is the most prevalent tick-borne infectious disease in the United States. In 2002, the cumulative total number of provisional cases of Lyme disease was 16,232. Provisional cases of Lyme disease in the United States in 2003 up to October 4, 2003, numbered 13,164.

The major goals of the NIAID Lyme disease research program are to develop better means of diagnosing, treating, and preventing this disease. To accomplish these objectives, the NIAID Lyme disease research portfolio includes a broad range of activities that are essential to increasing our understanding of the disease. The studies include both intramural and extramural research on animal models of disease, microbial physiology, molecular and cellular mechanisms of pathogenesis, mechanisms of protective immunity, vectors and disease transmission, efficacy of different modes of antibiotic therapy, and development of more sensitive and reliable diagnostic tests for both early (acute) and late (chronic) Lyme disease.

NIAID intramural investigators are studying Lyme disease on the NIH campus in Bethesda, Maryland, and at the Rocky Mountain Laboratories (RML) in Hamilton, Montana, where NIAID scientists discovered the etiologic agent *Borrelia burgdorferi* in the early 1980s.[39] RML scientists are using microarray technology to identify genes associated with unique aspects of the pathogenicity of Lyme disease and other relapsing fever microorganisms. Clinical investigators seek to better understand the natural history of chronic Lyme disease and possible causes for persisting symptoms. To this end, two clinical studies currently are ongoing at the NIH Clinical Center: one to evaluate and treat patients with classic Lyme disease, and the other to conduct a comprehensive clinical, microbiologic, and immunologic assessment of patients who have suspected chronic Lyme disease despite previous antibiotic therapy. In addition, NIAID clinical scientists assisted Tulane University colleagues in the development of a new laboratory test for detection of acute and persistent Lyme infection. The assay, called C6 peptide enzyme-linked immunosorbent assay (ELISA), is accurate and simple to perform. It can detect infection with both the U.S. and European strains of *Borrelia*, and it can be used to diagnose Lyme disease in patients who have received the Lyme disease vaccine. Lyme disease can be difficult to diagnose, especially in the later stages of infection when antibody concentrations are usually low. Laboratory testing, however, showed the C6 assay was able to detect disease-specific antibodies during both the early and late stages, with fewer false-positive results when compared with earlier screening methods. The new assay will be of enormous value in assessing patients' response to therapy.[40]

NIAID also supports an FY 2003 research initiative titled Partnerships for Hepatitis B and Vector-Borne Diseases. This initiative is an expansion of previous efforts that targeted animal vectors of disease and fostered development of partnerships among Government, academia, and the biotechnology and pharmaceutical industries. NIAID funded two grants on Lyme disease immunology and vaccine development under the 2003 initiative.

Lyme borreliosis and ehrlichiosis will continue to be areas of high priority for basic

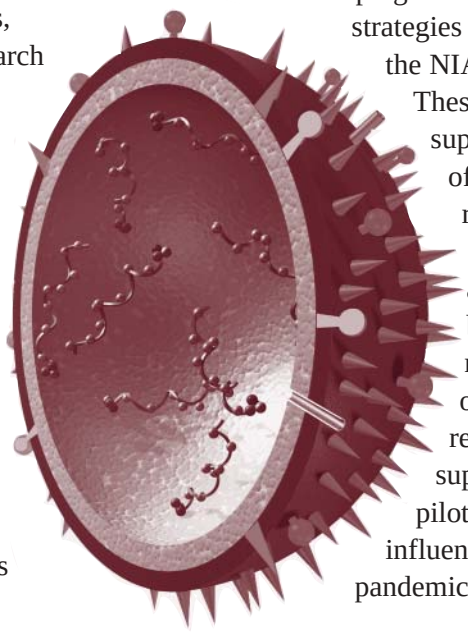
research for NIAID, especially with regard to (1) the characterization and treatment of acute and chronic infection; (2) the influence of co-infection with other vector-borne pathogens on the diagnosis, treatment, and severity of Lyme disease; and (3) the development of rapid, sensitive, and specific diagnostic tests and preventive strategies (e.g., vaccines and vector control measures).

Influenza

In the United States, pneumonia and influenza are the sixth leading cause of death, responsible for 3.7 percent of all deaths.[41] Research supported by NIAID has led to many new insights about how influenza causes disease.

The major goal of the NIAID influenza program is to support research leading to more effective approaches to control influenza virus infections. NIAID currently supports research in the following major areas:

- **Basic biology**—Primarily through R01 investigator-initiated grants, NIAID supports basic research on virus structure and function, viral pathogenesis, and the host response to infection.
- **Surveillance/ epidemiology**—NIAID supports research to better understand the natural history and emergence of influenza viruses with pandemic potential and to evaluate community-based strategies for interrupting the spread of influenza.
- **Public/private partnerships**—In 2000, NIAID awarded three challenge grants (required matching funds) to private-sector companies for the development of new vaccines against pandemic influenza strains. These companies are using live-attenuated viruses, virus-like particles, tissue culture substrates, and reverse genetics strategies to rapidly produce high-growth viruses for vaccine production. In 2003, NIAID awarded three cooperative agreements to industry for the development of a conserved protein-based influenza vaccine with the potential to protect against pandemic influenza viruses, a transepidermal DNA-based influenza vaccine, and a microchip-based rapid diagnostic test for influenza.
- **Drug discovery and evaluation**—NIAID supports the development of novel drugs against influenza and the evaluation of these new agents in both *in vitro* screening assays and in animal models.
- **Vaccine development and evaluation**—Developing new influenza vaccines and strategies has been a major focus of the NIAID influenza program. These strategies include supporting the development of live-attenuated and recombinant vaccines, immunomodulators and adjuvants, cell culture-based vaccines, and basic research aimed at optimizing the immune response. NIAID also supports the production of pilot lot vaccines against avian influenza subtypes of high pandemic potential.



An artist's rendition of a cross section of the influenza virus

In 2003, FDA approved FluMist, a new intranasally administered influenza vaccine, the development of which was supported by NIAID for more than 30 years, through both its intramural program and through extramural contracts and cooperative research and development agreements (CRADAs). Since the 1970s, NIAID has supported studies to evaluate the safety and immunogenicity of strains of the influenza virus that replicate only in the upper respiratory tract (temperature sensitive) and cause only minimal symptoms (attenuated), which could therefore be used as vaccines. In 1995, NIAID entered into a CRADA with Aviron for the commercialization of the product. Over the past 8 years, NIAID has conducted a series of clinical trials to evaluate the vaccine in children and in HIV-positive adults and children. In June 2003, FDA approved FluMist for healthy children and adults aged 5 to 49 years. The potential advantages of FluMist include the ease of administration and the ability to induce a broader immune response.

In addition, NIAID has begun an intramural program with the goal of developing vaccines against potential pandemic influenza strains. Aquatic birds serve as a reservoir from which new subtypes of influenza A viruses enter the human population. In the past 10 years, human infection with avian influenza viruses of three subtypes (H7, H5, and H9) have been detected on six occasions. An optimal public health response in the event of a potential pandemic requires that vaccines be available with minimum delay. NIAID intramural scientists and colleagues from CDC have initiated a collaborative, proactive approach to pandemic preparedness. They plan to generate and evaluate up to two dozen candidate vaccines against influenza A subtypes that are recognized to have pandemic potential. Using classic genetic recombination techniques, the team has developed a candidate H9N2 vaccine that has demonstrated efficacy in preclinical testing. Clinical studies of this candidate vaccine are planned for 2004.[42] A vaccine against H5N2 subtype influenza is in development.

In 2003, NIAID also expanded its Pandemic Preparedness in Asia contract with St. Jude Children's Research Hospital in Memphis. (The original award was made in 1998 for the surveillance and characterization of avian influenza viruses with pandemic potential in the live bird markets in Hong Kong.) Activities conducted under this expansion include establishing animal influenza surveillance sites in Asia, generating high-yield vaccine candidates against influenza strains with pandemic potential and accompanying reagents, supporting animal surveillance training in the Pacific Rim, and studying newly emerging influenza strains infecting swine in the United States.

The major focus of the NIAID influenza program will continue to be on basic and applied research that promises to further the development of new and improved vaccines and antiviral agents.

For more information on influenza, including weekly reports on flu activity, go to *www.cdc.gov/flu/weekly/fluactivity.htm.*

Prion Diseases

NIAID's DIR has a productive and growing program focused on transmissible spongiform encephalopathies (TSEs). These diseases also are called "prion diseases" because they are

known to be caused and transmitted by prion proteins, a new type of infectious agent discovered in the 1980s. Prion proteins enter cells and cause normal cellular proteins to adopt abnormal three-dimensional structures, which in turn leads to disease. TSEs are fatal neurodegenerative diseases and include scrapie, Creutzfeldt-Jakob disease (CJD), bovine spongiform encephalopathy (BSE or "mad cow" disease), and chronic wasting disease (CWD) of deer and elk. Since the onset of the BSE epidemic in the United Kingdom in the 1980s, the disease has resulted in the destruction of millions of animals in Europe. Because the BSE epidemic was temporally and geographically associated with the emergence of a variant form of CJD in humans, health officials believe the disease was spread to humans by infected beef. In May of 2003, the finding of BSE in a single cow in Canada resulted in a ban on exportation of certain live ruminants and ruminant products from Canada to the United States.

NIAID's intramural TSE research is aimed at increasing our fundamental understanding of prion protein (PrP) and the mechanisms responsible for the accumulation in nervous system cells of the abnormal form of PrP, which appears to underlie TSE pathogenesis. Studies also are ongoing to elucidate the mechanisms of cross-species transmission of TSE disease. This work is highly important in light of the epidemiology of variant CJD as well as the discovery of CWD in deer and elk herds beyond the areas in the western United States in which it was long known to exist. DIR scientists have conducted experiments that suggest that species once thought to be resistant to certain TSE strains can serve as lifelong carriers of the infection without ever becoming sick. Infrastructure improvements at NIAID's RML, including construction of new BSL-3 laboratory and animal facilities, have allowed expansion of TSE transmission studies. An important study to determine whether CWD PrP can be transmitted to nonhuman primates via oral or intracerebral routes has begun, using CWD samples obtained through NIAID's collaboration with the Wyoming Department of Health.

DIR scientists also have developed a high-throughput screening method to find compounds that show promise as potential TSE therapeutics. (See page 75.) Studies of the potential use of antibody and other vaccine-based therapies for TSEs are ongoing in NIAID laboratories. In addition, to advance earlier peptide studies, novel PrP peptides have been synthesized and are being evaluated for their ability to block the conversion of normal PrP to abnormal PrP-res *in vitro.* PrP peptides dispensed by direct injection or delivered by gene therapy might provide specific therapeutic treatment for TSE diseases. Promising compounds will be evaluated *in vivo* through a DMID contract with Utah State University. (See below.)

NIH provides grant support for investigator-initiated studies of CWD transmission that seek to better understand prion entry, trafficking, and neuroinvasion in the lymphoid system, which could provide a basis for development of diagnostic and intervention strategies. In addition, NIH has taken a number of actions in response to the Department's 2001 BSE/TSE Action Plan, including the following:

- NIAID awarded a 7-year, $8.4 million contract to Colorado State University to establish an emerging disease research center focused on CWD. Researchers at the center will isolate, identify, and

characterize strains of CWD; evaluate the potential for both inter- and intraspecies transmission; study the pathogenesis of CWD; perform preclinical, animal model-based evaluation of newly developed prevention measures or therapies for CWD; develop, analyze, and distribute reagents, infectious material, molecular clones, and transgenic mice to the research community; and implement a systematic approach to furthering our understanding of the ecologic and environmental factors influencing the emergence, spread, and distribution of CWD and of the basic epidemiology and clinical aspects of these diseases.

- NIH is evaluating potential anti-TSE compounds in animal models. Through expansion of an NIAID contract with Utah State University, candidate compounds are evaluated for efficacy in transgenic animals that have a shortened time to death. This model was established at Utah State in collaboration with NIAID's RML.